FDA U.S. FOOD & DRUG ADMINISTRATION

DEC 15 2017

Edwin R. Thompson, President
Pharmaceutical Manufacturing Research Services, Inc.
202 Precision Road
Horsham, PA 19044

Re: Docket No. FDA-2017-P-4352

Dear Mr. Thompson:

This letter responds to the citizen petition that Pharmaceutical Manufacturing Research Services, Inc. (PMRS) submitted to the Food and Drug Administration (FDA or the Agency) dated July 20, 2017 (Petition). In the Petition, you request that FDA:

- Refrain from approving pending [new drug application (NDA)] 209653 with the proposed indication of "management of moderate-to-severe pain when a continuous around-the-clock analgesic is needed for an extended period of time."

- Refrain from approving all other pending or future applications for opioids indicated for chronic use, including use over "an extended period of time," use for "long-term opioid treatment," or any other labeling for chronic use.

(Petition at 1) You contend that these indications are false and misleading and lack substantial evidence.[1]

We have carefully considered your Petition, which, among other things, addresses the critical issue of opioid addiction and abuse currently affecting the United States. We agree that opioid addiction and the resulting overdoses and deaths have created a national crisis, and note that the Agency is taking a variety of steps to address this public health concern.[2] As explained below, we deny your Petition because FDA believes it would be premature to make a determination at this time regarding your specific requests.

[1] You also submitted a petition dated March 6, 2017 that included similar arguments, requesting, among other things, that FDA revoke the approvals of extended-release or long-acting (ER/LA) opioids indicated for long-term use (March 2017 Petition). See docket no. FDA-2017-P-1359-0001, (available at www.regulations.gov). Your March 2017 Petition remains pending with the Agency, and we will respond to it as soon as we have reached a decision on your request.

[2] See, e.g., FDA's October 19, 2017 Response to PMRS Petition for Stay of Action at 6-8 (Docket No. FDA-2017-P-3064).

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I. BACKGROUND

A. Opioid Analgesic PMRs

Opioids are a class of powerful pain-relieving agents that include oxycodone, hydrocodone, and morphine, among others. When prescribed and used properly, opioids can effectively manage pain and alleviate suffering, clearly a public health priority. Opioids also have grave risks, the most well-known of which include addiction, overdose, and even death. The labeling for these products contains prominent warnings about these risks, among others. Most opioid-only drugs are controlled under Schedule II of the Controlled Substances Act, which imposes limitations on refills and strict recordkeeping, reporting, and physical security requirements.[3] This level of control reflects a finding that most opioid drugs have a "high potential for abuse" and that abuse "may lead to severe psychological or physical dependence."[4]

Opioid analgesic drugs are available, broadly speaking, as either extended-release/long-acting (ER/LA) or immediate-release (IR) products. Opioid analgesics have been approved for different conditions of use based on the data and information submitted by the sponsor of each drug product. Accordingly, product labeling may vary among approved opioid analgesic drugs, and such drugs may be prescribed for different patient populations.

In 2013, the Agency determined that more data are needed regarding, among other things, the relationship between opioid analgesic duration of use and serious adverse effects before the agency could determine whether additional action needed to be taken.[5] FDA exercised its authority under section 505(o)(3)(A)-(B) of the Food, Drug, and Cosmetic Act (FD&C Act) to require holders of approved ER/LA opioid analgesic NDAs to conduct studies (known as postmarketing requirements or PMRs) to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of opioid

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[3] 21 USC 801 et seq.; 21 CFR 1308.12. There are some opioids in Schedule III (e.g., buprenorphine) and Schedule IV (e.g., butorphanol).

[4] 21 USC 812(b)(2).

[5] FDA's action followed a July 26, 2012 citizen petition submitted by Physicians for Responsible Opioid Prescribing (PROP), in which PROP described concerns about the safety and efficacy of opioid analgesic drugs for long-term use in chronic, non-cancer pain. The petition (the 2012 PROP Petition) requested that the Agency: (1) "[s]trike the term 'moderate' from the indication [of opioid analgesics] for non-cancer pain"; (2) "[a]dd a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain"; and (3) "[a]dd a maximum duration of 90-days for continuous (daily) use" for non-cancer pain. FDA received more than 1900 comments on the 2012 PROP Petition. The Agency also received hundreds of comments relevant to these issues in the docket for a public hearing FDA held in February 2013, titled "Impact of Approved Drug Labeling on Chronic Opioid Therapy." See docket no. FDA-2012-N-1172 (available at www.regulations.gov). In 2013, the Agency denied PROP's request that FDA impose a maximum daily dose and maximum duration of use for opioid analgesics, and announced that the agency was requiring certain safety labeling changes (to more effectively communicate the serious risks of misuse, abuse, addiction, overdose, and death and the population in whom these drugs are appropriate in light of their serious risks) and requiring the PMRs described herein. See docket no. FDA-2012-P-0818-0793 (available at www.regulations.gov).

analgesics.[6] The PMRs currently require these sponsors to conduct ten observational studies pertaining to one or more of the known serious risks of opioid analgesics (misuse, abuse, addiction, overdose and death), as well as a clinical trial that requires an assessment of risk of developing hyperalgesia "following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain."[7] Four of the eleven PMRs explicitly state that the studies pertain to chronic or long-term opioid analgesic use, and FDA expects that chronicity of use will be an important factor in analyzing the study results for the PMRs.

B. Section 505(q) of the Federal Food, Drug, and Cosmetic Act

Section 505(q) of FD&C Act was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (Public Law 112-144, 126 Stat. 993). Section 505(q), as originally added by the FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on such a petition no later than 150 days after the date on which the petition is submitted.

II. DISCUSSION

In your Petition, you request that FDA: (1) refrain from approving pending NDA 209653 with the proposed indication of "management of moderate-to-severe pain when a continuous around-the-clock analgesic is needed for an extended period of time;" and (2) refrain from approving all other pending or future applications for opioid analgesics indicated for chronic use, including use over "an extended period of time," use for "long-term opioid treatment," or any other labeling for chronic use. In support of these requests, you argue, among other things, that there is insufficient scientific evidence of safety and effectiveness of opioid analgesics for long-term use.

FDA approves only those applications that meet the applicable statutory and regulatory requirements for approval (see generally sections 505(c) and 505(j) of the FD&C Act (21 U.S.C. 355(c) and (j)) and 21 CFR 314.50, 314.94, 314.105, 314.125 & 314.127). Approval decisions are based on the adequacy of the data and information supporting the particular application.

The majority of the PMRs discussed above are ongoing. FDA imposed these PMRs because, as explained at the time, we determined that more data are needed to assess the relationship between the duration of opioid analgesic use and the serious risks associated with opioid analgesic use. The PMRs obligate the ER/LA NDA holders to study the serious risks of misuse, abuse, hyperalgesia, addiction, overdose and death, particularly at increasing durations of use. FDA expects that the results of the studies required by these PMRs will be critical in informing

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[6] See https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf.

[7] See https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM484415.pdf at p. 7.

FDA's assessment of the relationship between the duration of use and the serious risks associated with opioid analgesic use, including appropriate labeling regarding the duration of use of opioid analgesics for treatment of pain.

As described above, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on your Petition within 150 days of submission. Therefore, we are denying your request to take the specified actions at this time insofar as we are continuing to consider, both in the context of application-specific reviews and ongoing PMRs, the issues you raised.

III. CONCLUSION

For the reasons explained above, your Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research